



CLDF

Chronic Liver Disease Foundation

3RD ANNUAL

LIVER C  NNECT

CONFERENCE



Is there a real difference
between ETV and TDF/TAF
in relapse and HCC?

W. Ray Kim, MD
Professor and Chief
Gastroenterology and Hepatology
Stanford University School of Medicine
wrkim@stanford.edu

Disclosure

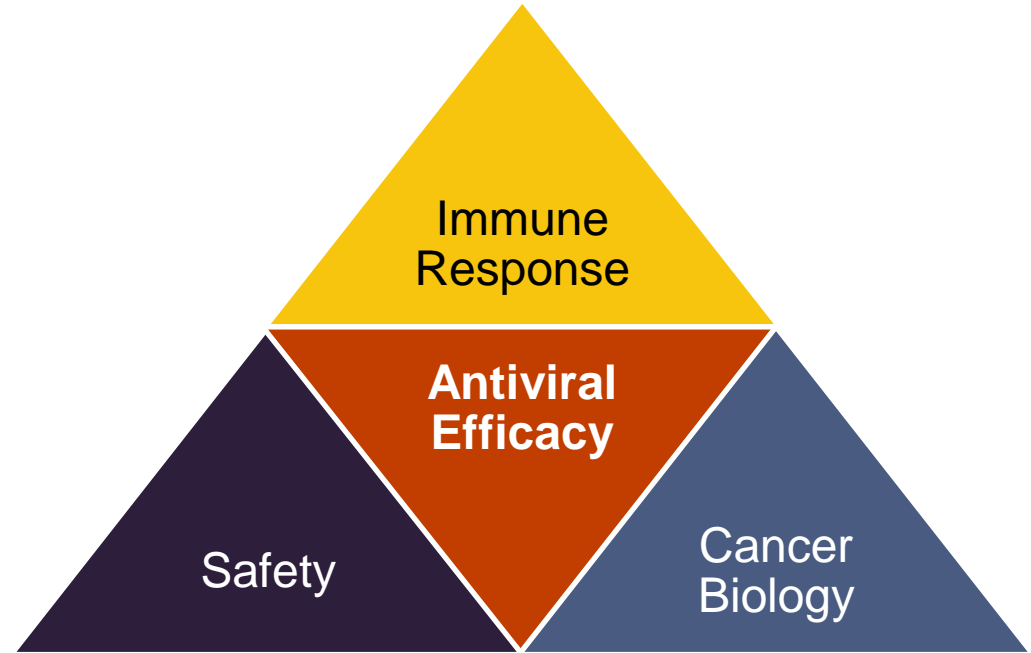


- Ad board and consulting for Gilead (no fee)

Potential Difference between ETV and TFV

Outline

- Antiviral Efficacy
- Relapse after Treatment Discontinuation
- Impact on HCC Risk
- Biological Basis
- Take Home



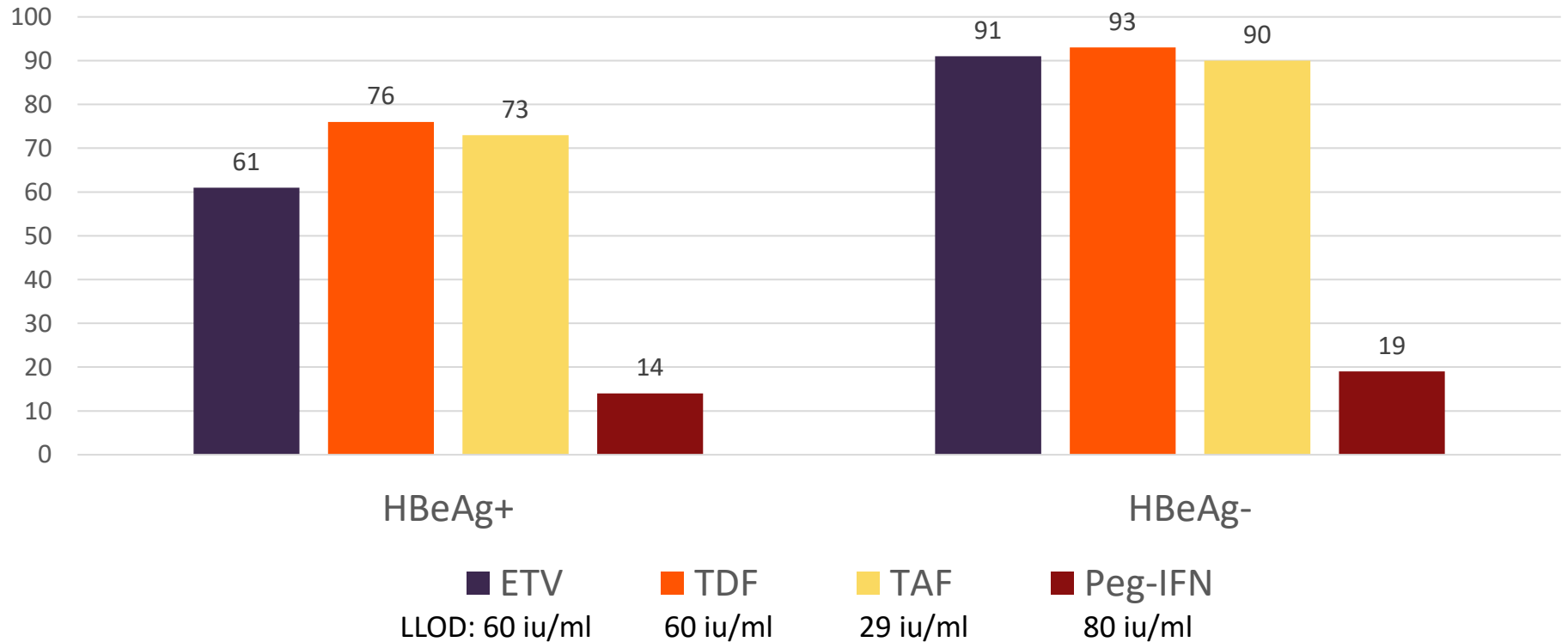
Case

- 30-year old Chinese American man, HBV diagnosed in childhood
- Treatment-naïve, HBeAg+

Timeline	HBV DNA	ALT	Action
0 (2011)	>55 M	108	ETV 0.5 QD
Mo 6	57,800	85	
Mo 12	118,000	78	

- What would you do?
 1. Stay on course for another 6 mo and reassess.
 2. Switch to tenofovir now.

AASLD Guidance: HBV DNA Suppression*

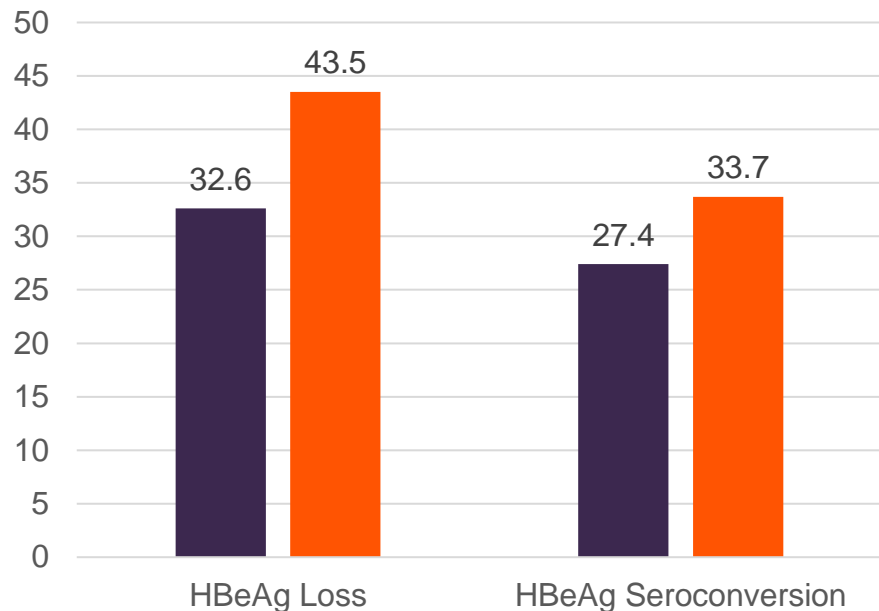
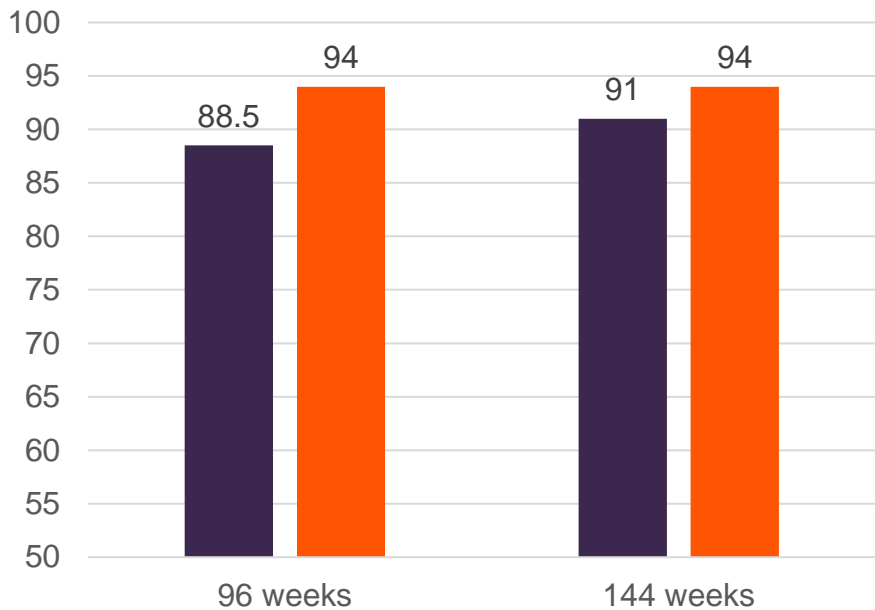


*Not head-to-head comparison

Efficacy of ETV versus TDF

- Randomized, head-to-head comparison (n=200 each arm)

~50% HBeAg positive (mean viral load: 7 log for eAg+, 5 log for eAg-)



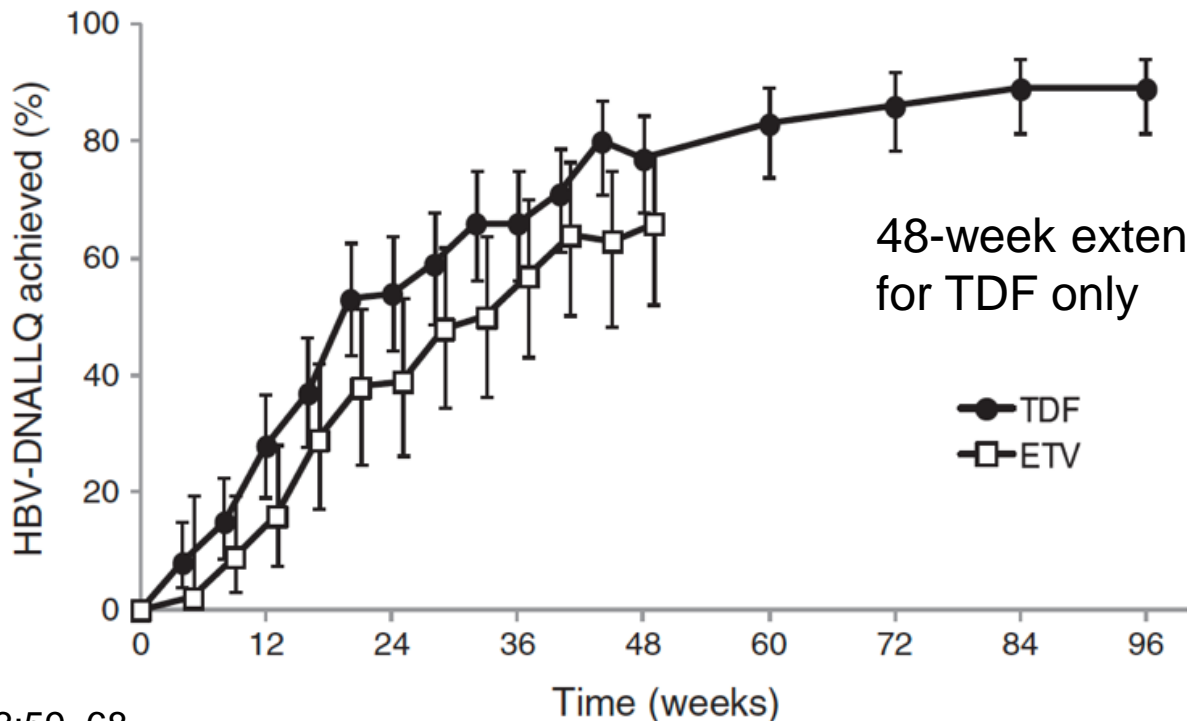
■ ETV ■ TDF

■ ETV ■ TDF

Efficacy of ETV versus TDF

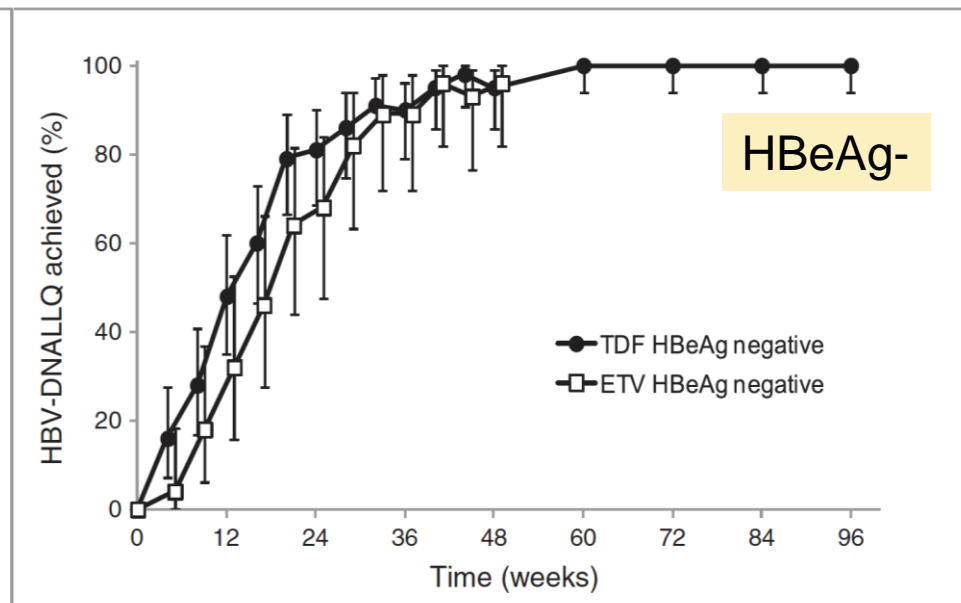
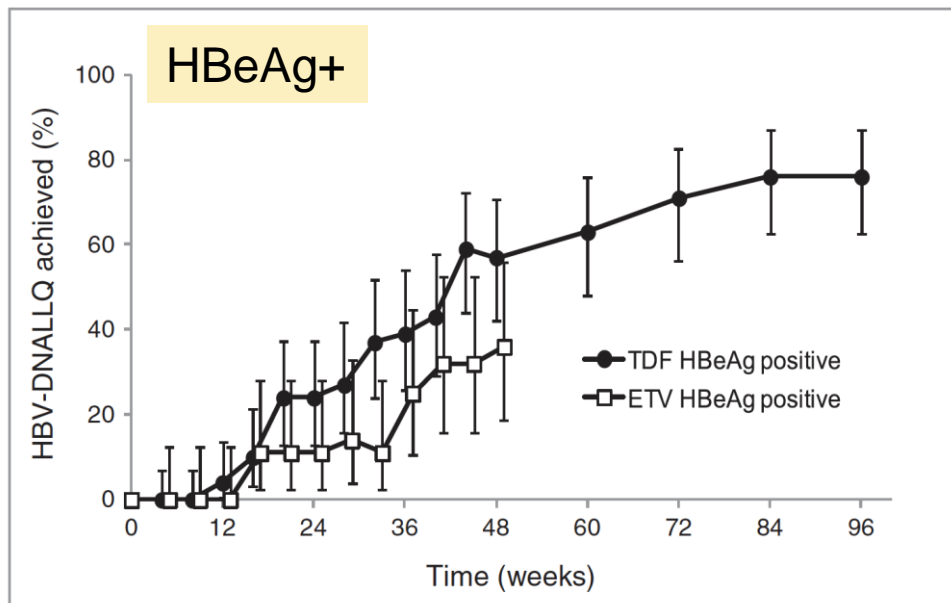
- Multicenter RCT for 48 weeks (pre-approval in Japan)

Primary end point:
Non-inferiority of
TDF versus ETV



Efficacy of ETV versus TDF

- Multicenter RCT for 48 weeks (pre-approval in Japan)
- Non-inferiority of TDF versus ETV



ETV versus TFV Score Card

	ETV	TFV
Efficacy	TFV Better (marginally, HBeAg+)	
Relapse		
HCC		

Case - continued

Timeline	HBV DNA	ALT	Action
0	>55 M	108	ETV 0.5 QD
Mo 6	57,800	85	
Mo 12	118,000	78	Switch to TDF
Mo 18	<40	74	Liver Bx: Gr 1, F0, Mild steatosis
Year 4	Und.	25	HBeAg-, HBeAb+

- Question: What would you do?
 1. Stop TDF after 6-12 months of consolidation
 2. Do not stop.

Case - continued

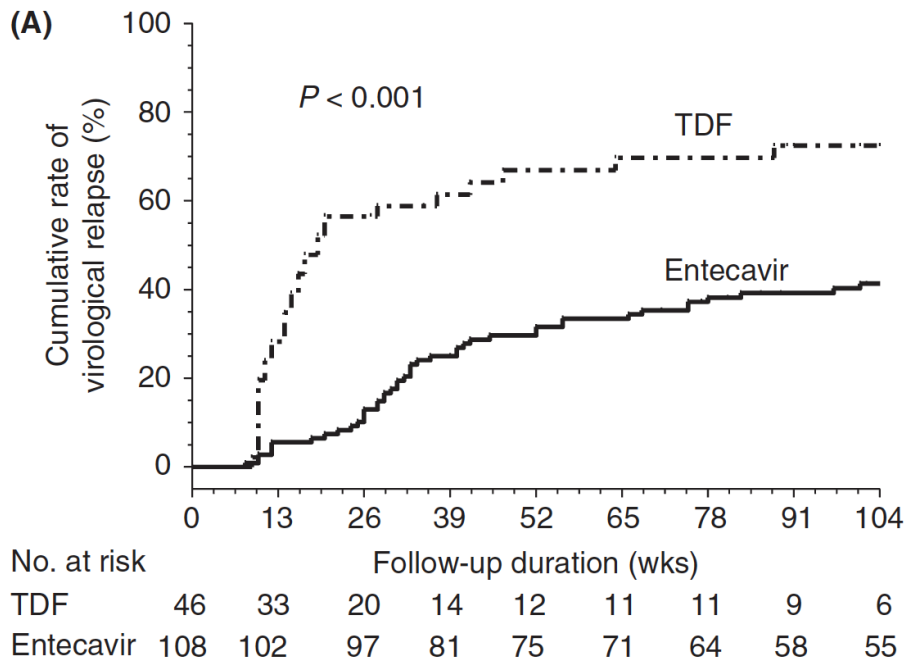


Timeline	HBV DNA	ALT	Action
0	>55 M	108	ETV 0.5 QD
Mo 6	57,800	85	
Mo 12	118,000	78	Switch to TDF
Mo 18	<40	74	Liver Bx: Gr 1, F0, Mild steatosis
Year 4	Und.	25	HBeAg-, HBeAb+
Year 6	Und.	29	TDF stopped
+ 3 Mo	7,282	51	
+ 4 Mo	205,728	542	TDF restarted (HBeAg- still)
Year 9	Und	34	qHBsAg 220 iu/ml

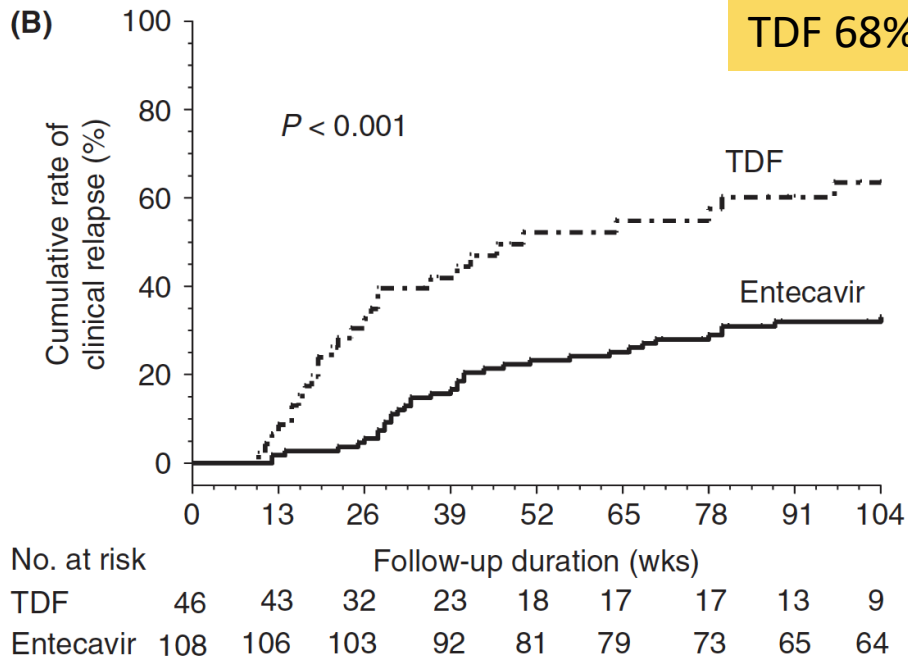


Relapse after Treatment Discontinuation: HBeAg+

DNA > 2000 iu/ml



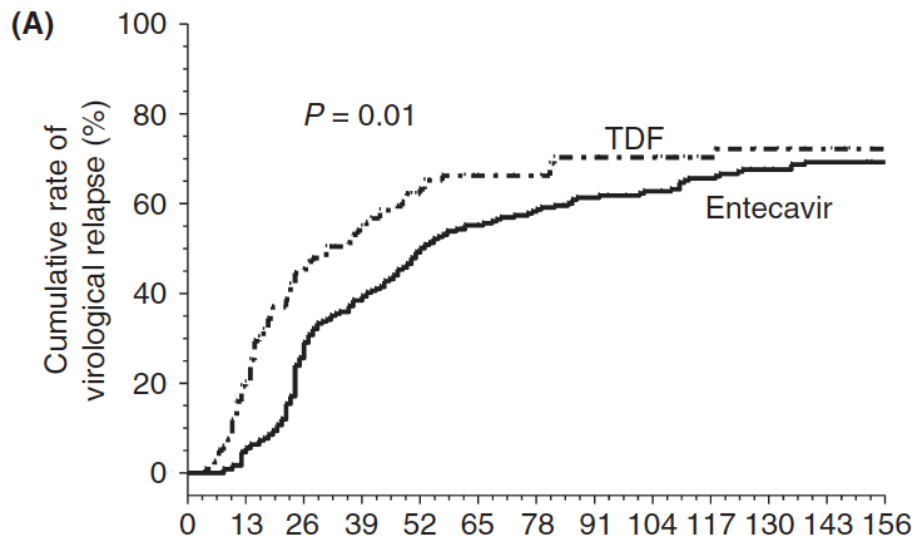
DNA > 2000 iu/ml
ALT > 80 U/l



Tx-naïve
ETV 79%
TDF 68%

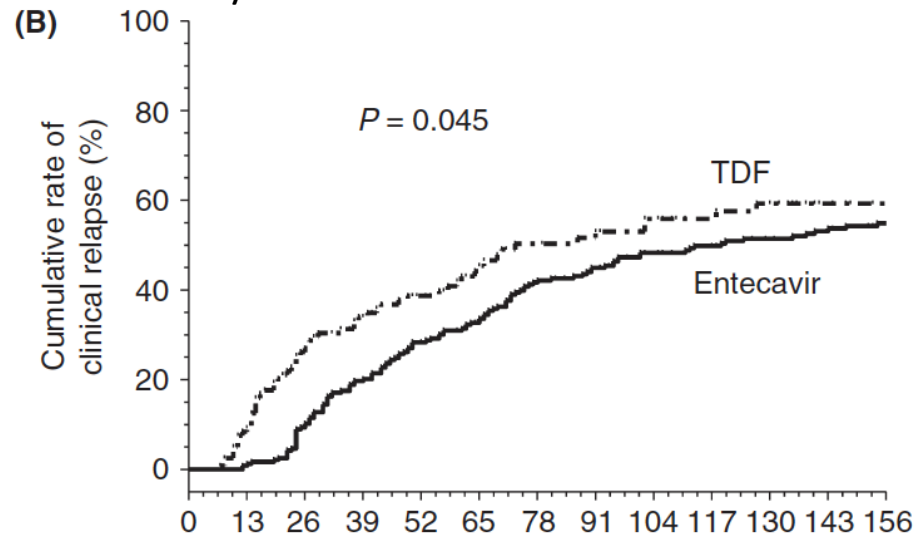
Relapse after Treatment Discontinuation: HBeAg-

DNA>2000 iu/ml



DNA>2000 iu/ml

ALT>80 U/l

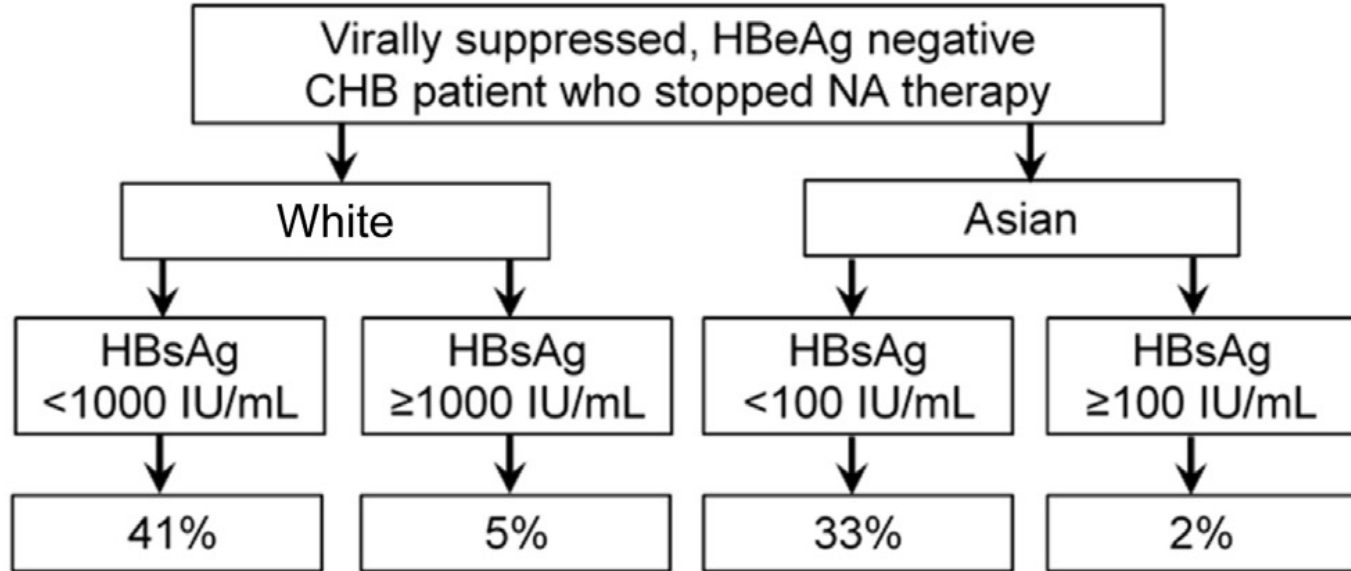


No. at risk	0	13	26	39	52	65	78	91	104	117	130	143	156
TDF	119	96	66	51	38	29	26	22	21	16	14	10	6
Entecavir	234	223	174	144	119	103	95	87	79	71	62	57	54

No. at risk	0	13	26	39	52	65	78	91	104	117	130	143	156
TDF	119	109	87	73	60	47	38	36	31	26	23	13	7
Entecavir	234	232	212	187	165	151	128	117	104	98	88	83	76

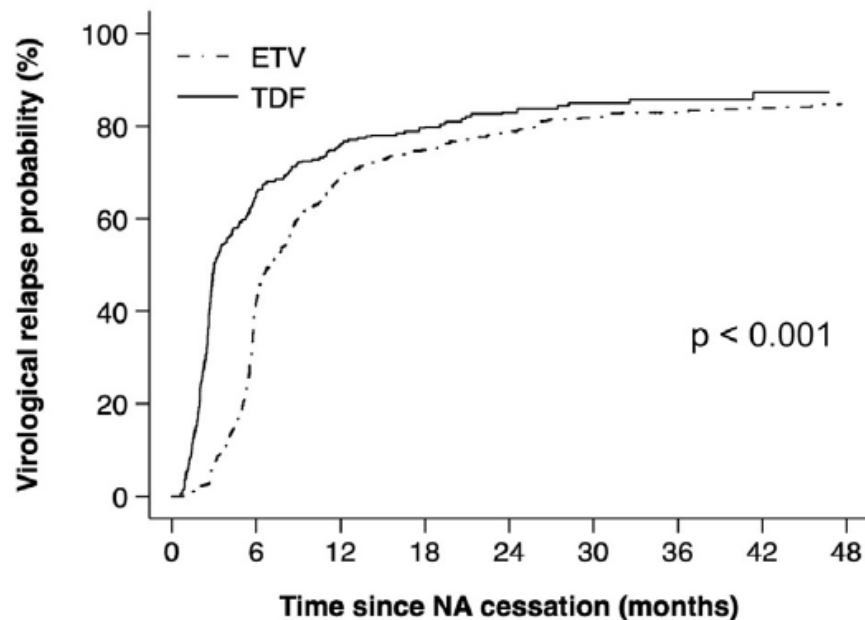
Antiviral Discontinuation (“Retract-B” Study)

- Global consortium data (n=1,552)
 - Various duration of Tx before discontinuation (median~3 years)
 - 88% Asian



ETV versus TDF in Retract-B Study

DNA>2000 iu/ml

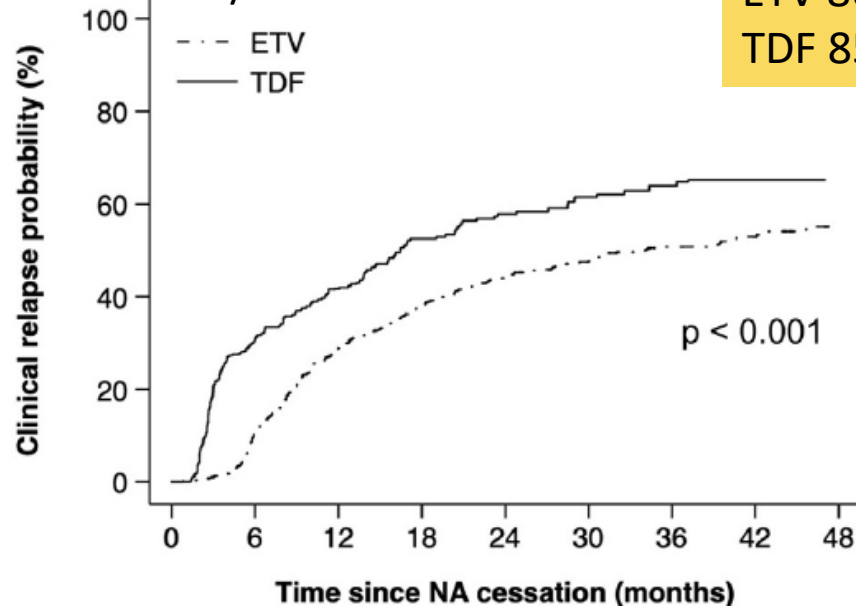


At risk

ETV	870.5	482.5	240.5	174.8	126.6	88.9	71.2	59.7	47.4
TDF	357.0	122.4	76.5	51.4	31.0	23.5	15.3	11.5	6.8

DNA>2000 iu/ml

ALT>80 U/l

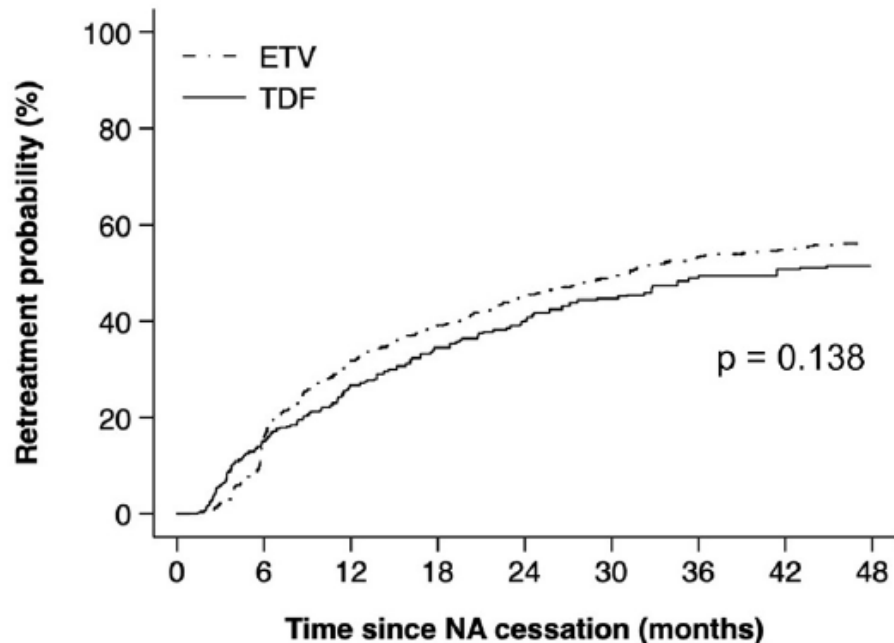


At risk

ETV	870.5	644.8	439.1	339.3	262.0	203.5	165.6	137.4	103.9
TDF	357.0	237.8	182.1	120.8	85.3	68.4	46.8	35.0	23.3

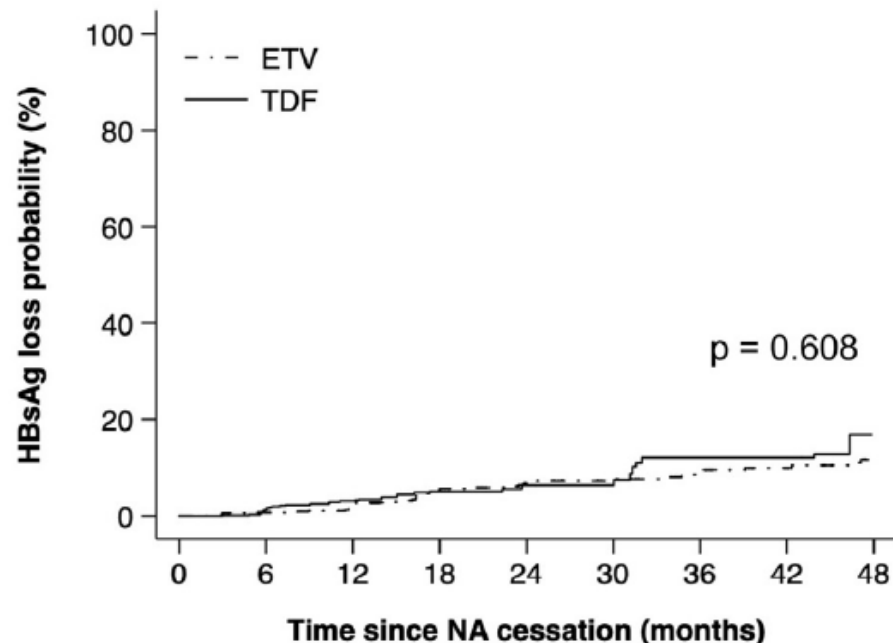
Tx-naïve
ETV 86%
TDF 85%

ETV versus TDF in Retract-B Study



At risk

ETV	870.5	702.9	533.9	428.7	331.9	266.9	214.0	182.2	141.9
TDF	357.0	297.6	240.2	174.7	135.8	109.0	75.8	51.3	35.0



At risk

ETV	870.5	702.9	533.9	428.7	331.9	266.9	214.0	182.2	141.9
TDF	357.0	297.6	240.2	174.7	135.8	109.0	75.8	51.3	35.0

ETV versus TFV Score Card

	ETV	TFV
Efficacy	TFV Better (marginally, HBeAg+)	
Relapse	ETV Better (emerging data)	
HCC		

Risk of HCC: TDF versus ETV (US Data)

Incidence of HCC in CHB Patients Initiating Antiviral Therapy

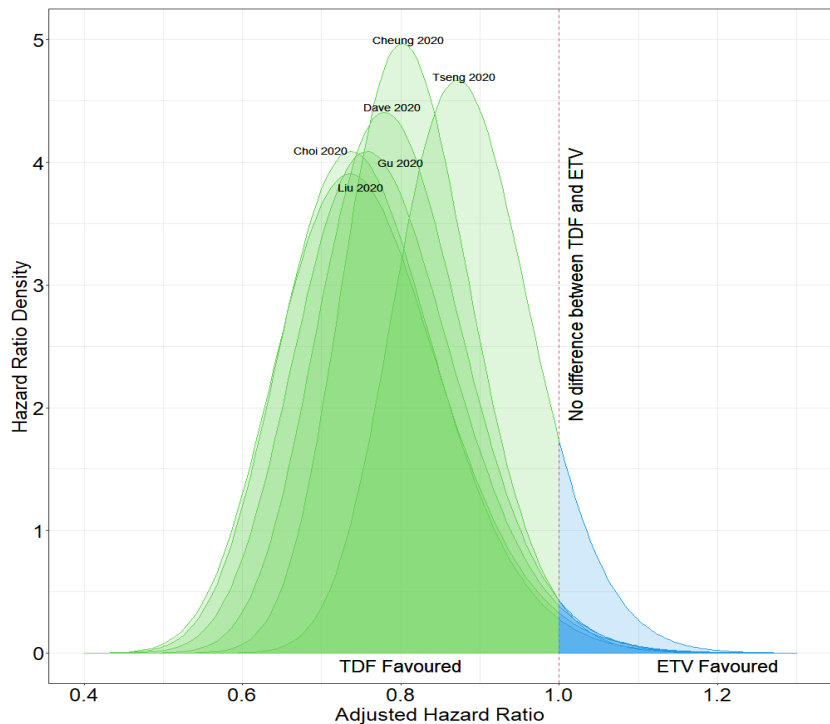
Study Population	Observation	Outcome
<p data-bbox="123 467 529 596">IQVIA PharMetrics Plus™ Claims Database 2006-2019</p> <p data-bbox="117 685 548 907">Adults with chronic hepatitis B without prior therapy (n=10,061)</p>	<p data-bbox="678 418 1170 565">Initiation of entecavir (ETV) or tenofovir disoproxil fumarate (TDF)</p> <p data-bbox="683 659 913 696">ETV (n=3,934)</p> <p data-bbox="774 740 1099 773">Mean follow-up: 752d</p> <p data-bbox="683 816 915 853">TDF (n=6,127)</p> <p data-bbox="774 897 1099 930">Mean follow-up: 791d</p>	<p data-bbox="1340 484 1846 615">Occurrence of HCC (versus liver transplant, unrelated deaths, and new antiviral therapy)</p> <p data-bbox="1379 703 1619 746">0.62/100 py</p> <p data-bbox="1379 856 1619 899">0.30/100 py</p> <p data-bbox="1676 779 1870 823">sHR=0.58</p>

py = person years

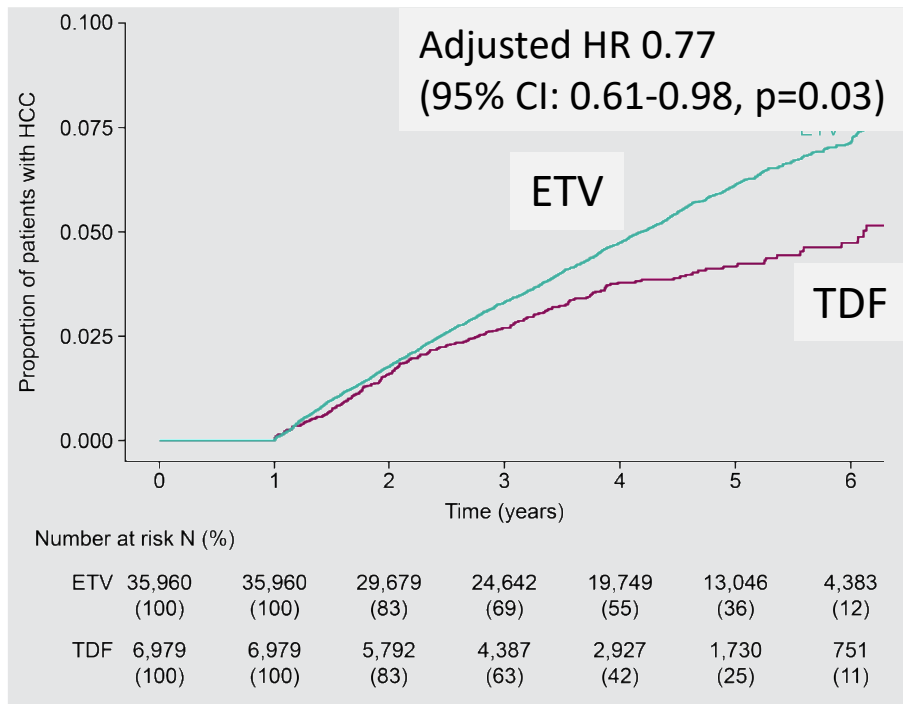
sHR = subdistribution hazard ratio

Meta-analysis: Antiviral Selection and HCC Incidence

- Up to 32 papers on the topic with 6 meta-analysis since 2019



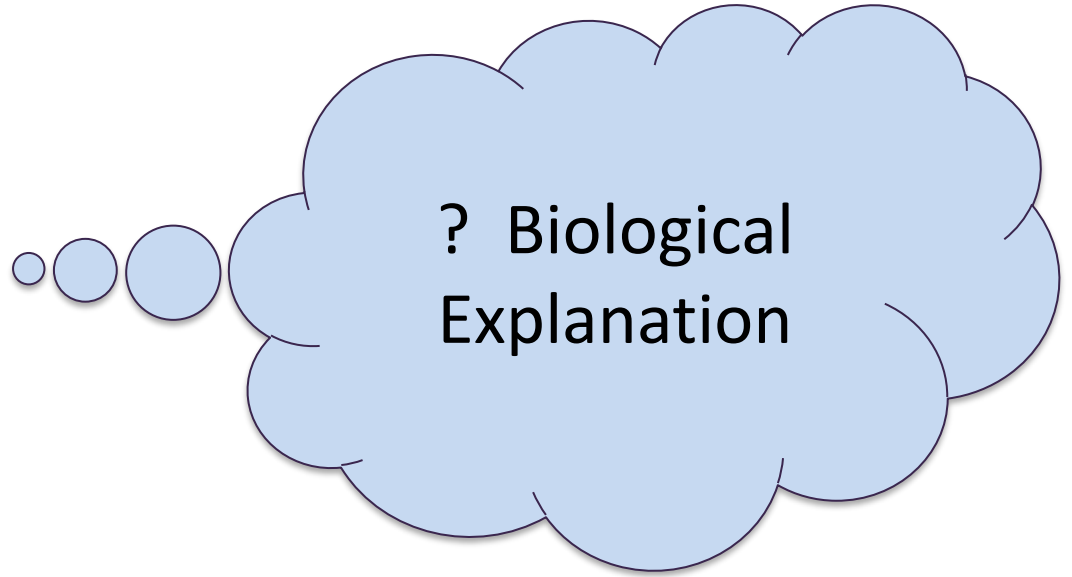
Individual patient meta-analysis (n=42,939)



ETV versus TFV Score Card

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Efficacy	TFV Better (marginally, HBeAg+)	
Relapse	ETV Better (emerging data)	
HCC	TFV Better (observational data)	

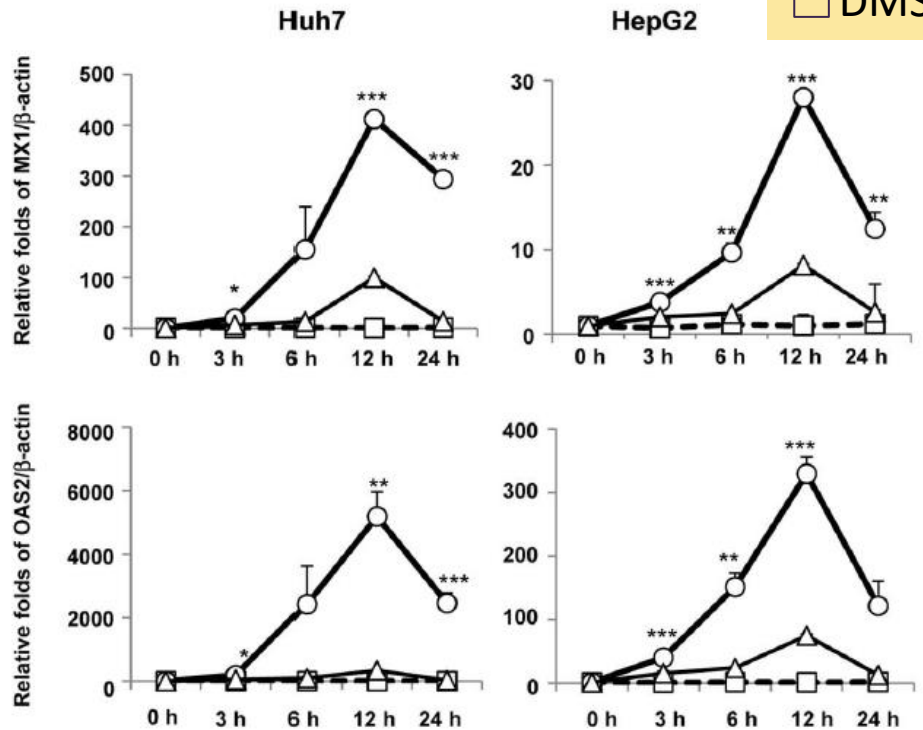
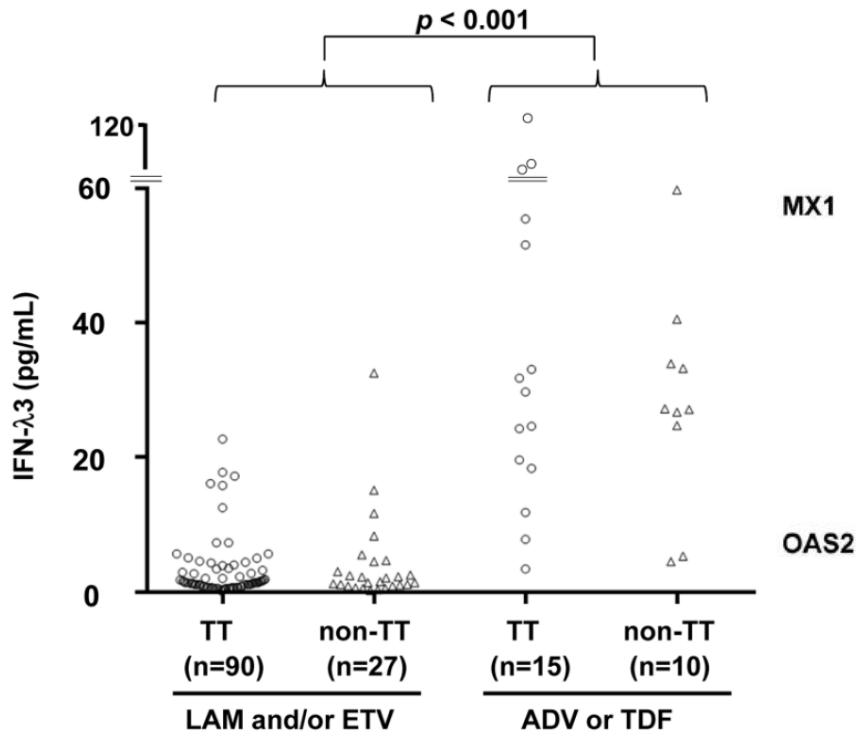
Why would this be?



Differential Induction of IFN-λ3

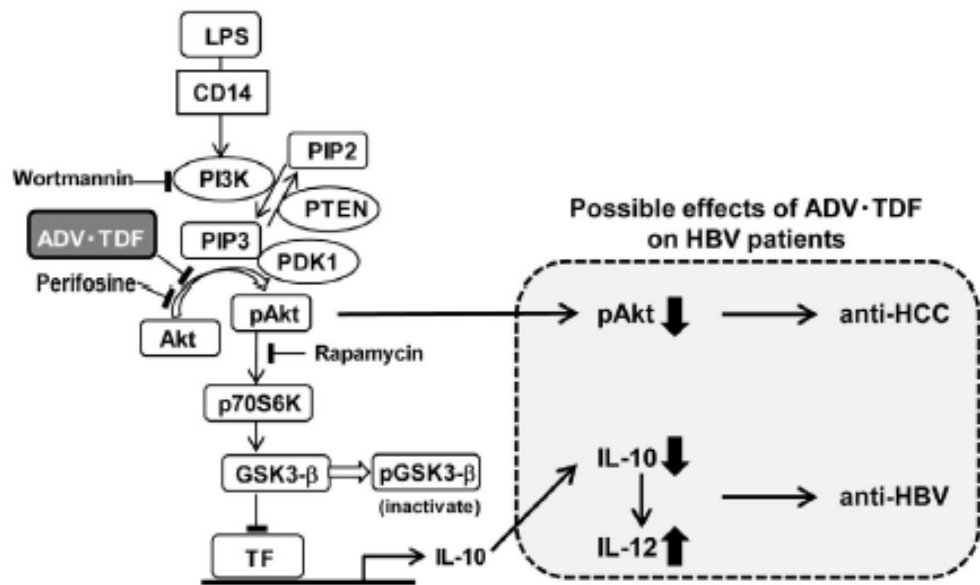
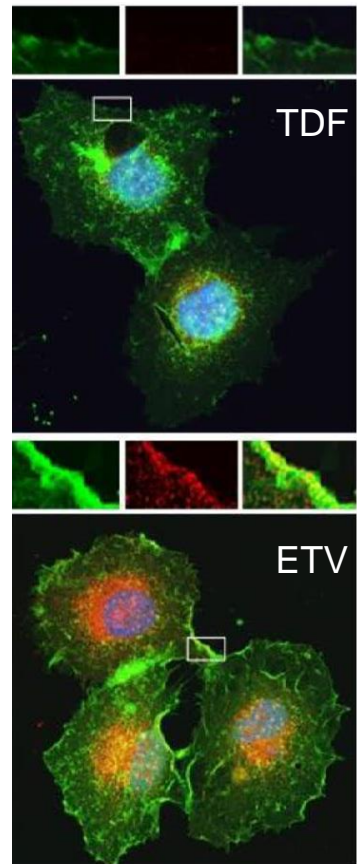
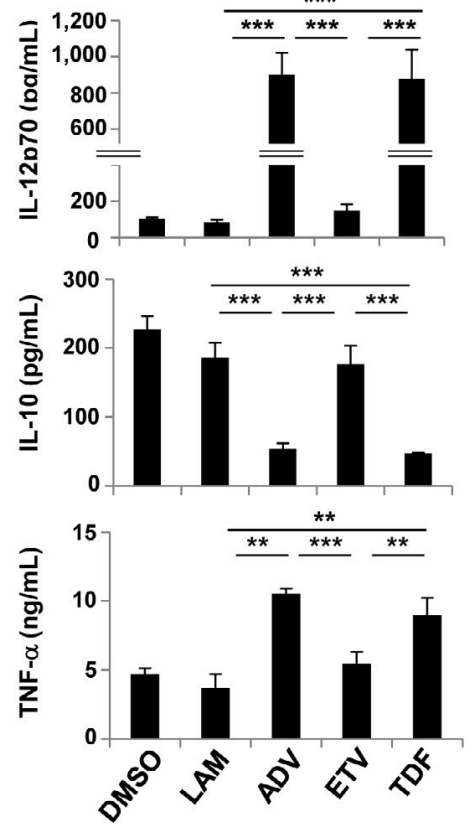
- IFN-λ3 (IL-28b) suppresses HBV replication via multiple mechanisms
- Nucleotide analogues induce IFN-λ3 better than nucleoside analogues.

○ ADV
 △ ETV
 □ DMSO



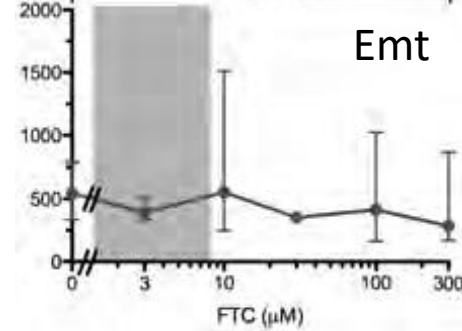
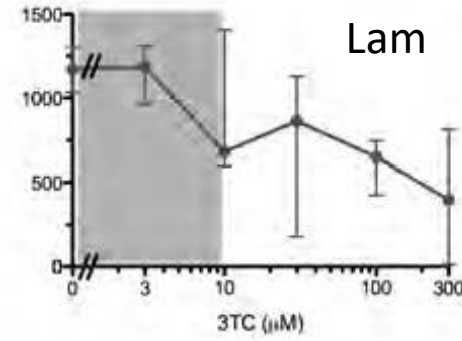
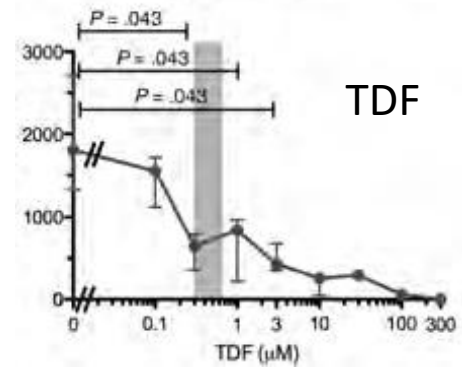
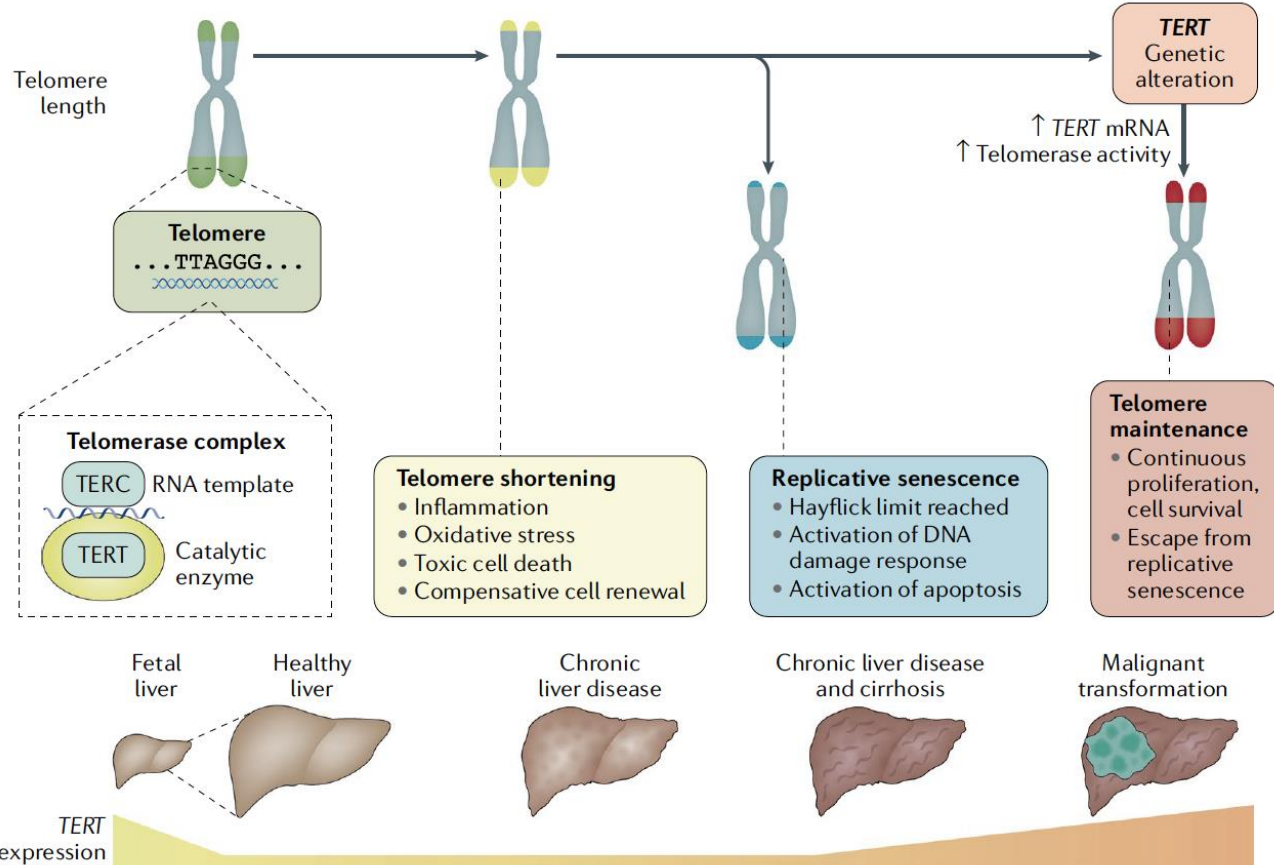
IL-10 versus IL-12

A



Akt
pAkt
Nucleus

Telomerase Inhibition



ETV versus Tenofovir: Clinical Implications Today

- Despite laboratory data suggesting advantage for TFV, clinical data are mixed.
- For high viral load HBeAg+ patients, TFV may be preferred for better control of viremia.
- For relapse, further data are needed: ?switch from TFV to ETV before discontinuing therapy.
- For the HCC question:
 - New high-risk patient (e.g., high viral load, fibrosis, family history):
 - 20%+ reduction in HCC risk may be meaningful.
 - Preferring TFV may be reasonable.
 - Existing stable patients: Smaller benefits, Insufficient data to switch to TFV
 - Patient preference

	ETV	TFV
Efficacy	TFV Better (marginally, HBeAg+)	
Relapse	ETV Better (emerging data)	
HCC	TFV Better (observational data)	

